REMARKS

Status of the Claims

Claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 are pending in the application. Claims 1, 6, 7, 10, 23 and 33-37 have been amended. New claims 38-43 have been presented. Claims 1-4, 6-10, 12, 23-26, 28-29 and 33-37 have been rejected. No new matter has been added.

In light of the amendments and remarks presented herein, Applicants respectfully request reconsideration and allowance of claims 1-4, 6-10, 12, 23-26, 28-29 and 33-43.

Amendment to the Claims

Claims 1, 6, 7, 10, 23 and 33-37 have been amended. Amendments to the claims have been made to clarify Applicants' invention. Support for the amendments can be found throughout the specification and in the claims as originally filed, as well as in paragraphs [0117], [0118] and [0124], in particular. No new matter has been added.

New Claims

New claims 38-43 have been added. New claims 38-43 are directed to specific cell types that comprise the first population of cells (claims 38-41) or the second population of cells (claims 42-43). Support for the new claims can be found in original claims 1, 6, 7 and 12.

The Invention

The current invention is directed to a method of organ augmentation that utilizes two populations of cells with distinct functions, a *first population of cells* that is *transiently transfected* to express an *angiogenesis modulating agent*, and a *second population of cells to be assimilated* at the target site. Independent claim 1 is directed to a method of organ augmentation using the two populations of cells, the first population transiently transfected to express VEGF and the second population to assimulate at the target region, implanted together in an *injectable polymer matrix* inducing *assimilation and differentiation* at the target region. Independent claim 23 is directed to a method that involves implanting a *transiently transfected first population* of

cells with a *second population* of cells in an organ construct to *assimilate and differentiate* at the target site.

Nowhere in the references cited by the Examiner, either alone or in combination, is there a teaching or suggestion of the claimed invention.

Rejection under 35 U.S.C. 103(a)

Claims 1-3, 6-8, 10, 12, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view of Lu et al. (2001), Atala et al. (US Patent 6,479,064), Springer et al. (2000), Rinsch et al. (2001) and Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants respectfully disagree.

Naughton (2003/0007954) teaches a three-dimensional stromal tissue implant. In the reference, stromal cells are grown on a biocompatible structure or framework and the implant is used for implant into a single location. However Naughton fails to teach or suggest two separate populations of cells, *transiently transfecting* a first population to express the angiogenesis modulating agent VEGF and suspending the first population with a second population of cells in an *injectable polymer matrix* whereby assimilation and differentiation of the second population of cells occurs at the target region.

The Office Action cites an additional 5 references to remedy the deficiencies of Naughton et al. Specifically, the Office action cites Lu et al. to teach retroviral transduction of myoblasts to express VEGF in bioartificial muscle tissues, Atala et al. to teach preparation of an artificial organ construct using matrices seeded with endothelial cells and Springer et al., Rinsch et al. and Penn et al. to teach encapsulation of VEGF expressing myoblasts and transient transfection. However, none of the references alone or in combination remedy the deficiencies of Naughton et al. to teach two separate populations of cells, *transiently transfecting a first population* of cells to express the angiogenesis modulating agent VEGF and suspending the first population with a *second population of cells* in an *injectable polymer matrix* thereby inducing *assimilation and differentiation of the second population* at the target region to render claim 1 and dependent claims obvious.

The Examiner has stated that "no specific deficiency or limitation not clearly taught by the cited references has been particularly pointed out by the Applicants." However, nowhere in the references is there any teaching or suggestion to a method that uses two separate populations and *transiently transfecting a first population* of cells to express the angiogenesis modulating agent VEGF and suspending the first population with a *second population of cells* in an *injectable polymer matrix* thereby inducing *assimilation and differentiation of the second population* at the target region.

KSR Int'l Corp. v. Teleflex, Inc. requires that an Examiner provide "some articulated reasoning with some rationale underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Specifically, an Examiner must "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* See also, MPEP 2143. Without such reasoning, one cannot conclude that the claim would have been obvious to one of ordinary skill in the art.

The Examiner states that the inclusion of myoblasts as the particular species of cardiac muscle cells, and vascular endothelial cells as the particular species of endothelial cells would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. However, the Examiner has advanced no reason why one of ordinary skill in the art with knowledge of Naughton would conclude that the use of two separate populations of cells, a *first population that is transiently transfected* to express the angiogenesis modulating agent VEGF and a *second population of cells to assimilate and differentiate* combined with the first population in an *injectable polymer matrix* would have been obvious.

Here, the only reasoning provided by the Office Action for combining Naughton with the other references is hindsight reconstruction, since the other references teach aspects of the Applicants' invention. The Examiner is relying on the present invention as an instruction manual or "template" to piece together various disclosures from the prior art to arrive at the claimed invention.

The Examiner states that hindsight reconstruction is proper, "so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure." However, as no reason has been provided for reconstructing the Applicants' invention by piecing together various disclosures, only the instructions gleaned from the Applicants' disclosure serve as a reason to combine the references in such a way. Therefore, hindsight reconstruction is improper.

Moreover, the additional references fail to remedy the deficiencies of Naughton and do not amount to a teaching or suggestion of claim 1 or dependent claims therefrom. In fact, none of the references alone or in combination teach or suggest claim 1 or dependent claims therefrom.

Amended claim 10 is directed to encapsulating the first population of cells. As mentioned above, the only reason the Examiner has cited Springer et al. and Rinsch et al. is because they teach encapsulation of myoblasts. Penn et al. was further cited as teaching transient transfection of myoblasts.

The Examiner further states that "one of ordinary skill in the art would have been motivated to co-implant the microencapsulated myoblasts of Springer et al. and Rinsch et al., modified per suggested method of Penn et al., for the purpose of enhancing cell survival and assimulation of the tissue construct of Naughton et al. into the ischemic tissue site and to promote angiogenesis in and around the ischemic tissue site."

The reasoning in the Office Action only amounts to hindsight reconstruction and none of the references teach or suggest *transiently transfecting* a first population of cells and *encapsulating the transiently transfected* cells. Nor do the references teach any of the other limitations recited in claim 10 and dependent claims therefrom, such as *suspending the encapsulated first population with the second population* of cells in an *injectable polymer matrix* and *inducing assimulation and differentiation of the second population* of cells in the target region.

Moreover, the Examiner ignores the fact that the Naughton reference actually *teaches away* from the present invention. Specifically, Naughton teaches:

> Recently, a gene-therapy approach was used to deliver VEGF by injection of retroviral vectors that targeted heart tissue and resulted in VEGF production (Losordo et al., 1998, Circulation 98:2800-2804). This in situ method improved blood flow and subjective symptoms in patients, suggesting that local delivery of a growth factor such as VEGF to promote angiogenesis in heart tissues may be of therapeutic value in the treatment of certain heart conditions. *However, such gene therapy techniques utilizing retroviral vectors present certain inherent risks and safety concerns.* In addition, gene therapy-type approaches present a number of *unresolved, problematic technical hurdles such as low transfection levels for recipient cells, construct instability and long-term expression of the desired gene product from the transfected cells.*

See Naughton at page 1, paragraph [0006]. Emphasis added.

Naughton clearly rejects the approach of using transfected cells to express angiogenesis modulating agents, such as VEGF. In fact, Naughton's principal contribution to the art lies in teaching that a three-dimensional stromal tissue bed, preferably including fibroblasts, will intrinsically express and secret VEGF. Thus, one skilled in the art would not have been lead to supplement Naughton's construct with a *separate* population of cells *genetically engineered* to express angiogenesis modulating agents, much less an *encapsulated* population or one that would express such agents *transiently*.

Therefore Applicants respectfully request reconsideration and withdrawal of the obviousness rejection to claims 1-3, 6-8, 10, 12, 34 and 35.

Claims 1-3, 6-10, 12, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view of Lu et al. (2001), Atala et al. (US Patent 6,479,064), and MacLaughlin et al. (US Patent 6,692,738), and further in view of Springer et al. (2000), Rinsch et al. (2001) and Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants respectfully disagree.

Naughton et al., Lu et al., Atala et al., Springer et al., Rinsch et al. and Penn et al. are all described above. MacLaughlin et al. describe implantable tissue matrices seeded with genetically engineered cells.

The Office Action asserts that Naughton et al. does not specify collagen type I as a scaffold material and further cites Maclaughlin et al., as well as Lu et al., Atala, Springer et al., Rinsch et al. and Penn et al. to remedy the deficiencies. However, combining Naughton et al. with the other references still does not reconstruct the claimed invention of the current application, that includes a method utilizing two separate populations and comprises *transiently transfecting a first population of cells* to express the angiogenesis modulating agent VEGF and combining the first population of cells with a *second population of cells* in an *injectable polymer matrix* and inducing *assimilation and differentiation* of the second population of cells at a target region.

The Examiner states that "because Naughton et al. and MacLaughlin et al. both disclose scaffold materials which are appropriate for formation of engineered tissue constructs, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute any of the scaffold materials for another."

However, the Office Action fails to recognize that the references combined with Naughton still do not yield the invention of claim 1 or dependent claims therefrom. Namely, a method utilizing two separate populations and comprises *transiently transfecting a first population of cells* to express the angiogenesis modulating agent VEGF and combining the first population of cells with a *second population of cells* in an *injectable polymer matrix* and inducing *assimilation and differentiation* of the second population of cells at a target region.

Moreover, the Office Action fails to provide a reason why one of ordinary skill in the art with knowledge of Naughton et al. would look to the other references to combine the elements in the same way as the claimed invention. The only reason presented is hindsight reconstruction. As it is improper to pick and choose features from the prior art in such a manner, hindsight reconstruction is improper.

Additionally, as noted above, Naughton *teaches away* from the use of a *separate population* of cells genetically engineered to *transiently express angiogenesis modulating agents*. The previously presented arguments are incorporated by reference for the sake of brevity.

As the Office Action has improperly rejected the Applicants' invention through hindsight reconstruction, as well as the cited references fail to teach or suggest claim 1 and dependent claims therefrom, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection to claims 1-3, 6-10, 12, 34 and 35.

Claims 1-4, 6-8, 10, 12, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view of Lu et al. (2001), Atala et al. (US Patent 6,479,064), further in view of Springer et al. (2000), Rinsch et al. (2001) and Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants respectfully disagree.

This rejection is essentially a reiteration of the first 103 rejection with the addition of claim 4. The arguments presented above are the same for claim 4 as for claim 1. Moreover, none of the cited references teach or suggest *transiently transfecting a first population of cells comprising vascular endothelial cells* to express the angiogenesis modulating agent VEGF and combining the first population of cells with a *second population of cells* in an *injectable polymer matrix* and inducing *assimilation and differentiation* of the second population of cells at a target region as recited in claim 4.

Since the cited references, alone or in combination, fail to teach or suggest the invention of claim 1 as well as dependent claims, claims 1-4, 6-8, 10, 12, 34 and 35 are unobvious and patentable.

Claims 23, 26, 28-29 and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view of Springer et al. (2000), Rinsch et al. (2001) and Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants respectfully disagree.

Naughton (2003/0007954) teaches a three-dimensional stromal tissue implant capable of secreting VEGF. In the reference, stromal cells are grown on a biocompatible structure or framework and the implant is used for implant into a single location. However Naughton fails to teach or suggest two separate populations of cells, *transiently transfecting* a first population to express an angiogenesis modulating agent, culturing a *second population of cells* on a *matrix material* to produce an organ construct and implanting the organ construct with the first population of cells whereby *assimilation and differentiation* of the second population of cells occurs at the target site.

The Office Action further cites Springer et al., Rinsch et al. and Penn et al. to remedy the deficiencies of Naughton et al. Specifically, the Office action cites Springer et al., Rinsch et al. and Penn et al. to teach encapsulation of VEGF expressing myoblasts and transient expression. However, none of the references alone or in combination remedy the deficiencies of Naughton et al. to teach *transiently transfecting a first population* to express an angiogenesis modulating agent, culturing a *second population of cells* on a *matrix material* to produce an organ construct and implanting the organ construct with the first population of cells whereby *assimilation and differentiation of the second population* of cells occurs at the target site to render claim 23 and dependent claims obvious.

As stated above, the only reasoning provided by the Office Action for combining Naughton with the other references is hindsight reconstruction, since the other references teach elements of the Applicants' invention. However, no reason has been given why one of ordinary skill in the art would combine Naughton's tissue constructs with a second population of cells. The Examiner is relying on the present invention as an instruction manual or "template" to piece together various disclosures from the prior art to arrive at the claimed invention.

Moreover, the additional references fail to remedy the deficiencies of Naughton and do not amount to a teaching or suggestion of the claimed invention. In fact, none of the references alone or in combination teach or suggest claim 23 or dependent claims.

Amended claim 33 is directed to encapsulating the first population of cells. As mentioned above, the only reason the Examiner has cited Springer et al. and Rinsch et al. is because they teach encapsulation of myoblasts. Penn et al. was further cited as teaching transient transfection of myoblasts.

The Examiner further states that "one of ordinary skill in the art would have been motivated to co-implant the microencapsulated myoblasts of Springer et al. and Rinsch et al., modified per suggested method of Penn et al., for the purpose of enhancing cell survival and assimulation of the tissue construct of Naughton et al. into the ischemic tissue site and to promote angiogenesis in and around the ischemic tissue site."

The reasoning in the Office Action only amounts to hindsight reconstruction and none of the references teach or suggest *transiently transfecting* a first population of cells and *encapsulating the transiently transfected* cells. Nor do the references teach any of the other limitations recited in claim 33 and dependent claims therefrom, such as two separate populations of cells, *transiently transfecting* a first population to express an angiogenesis modulating agent, *encapsulating the transfected first population of cells*, culturing a *second population of cells* on a *matrix material* to produce an organ construct and implanting the organ construct with the *encapsulated first population* of cells whereby *assimilation and differentiation* of the second population of cells occurs at the target site.

Furthermore, as noted above, Naughton actually *teaches away* from the use of a *separate population* of cells genetically engineered to *transiently express angiogenesis modulating agents*. Instead Naughton teaches that cells intrinsically expressing VEGF are preferable to circumvent *unresolved, problematic technical hurdles* presented by gene therapy type approaches. Thus, one skilled in the art would not have been lead to supplement Naughton's construct with a *separate* population of cells *genetically engineered* to express angiogenesis modulating agents,

much less an *encapsulated* population or one that would express such agents *transiently*. The previously presented arguments are incorporated by reference for the sake of brevity.

Therefore, in light of the remarks above, claims 23, 26, 28-29 and 33-37 are nonobvious and are patentable over the prior art. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection .

Claims 23-26, 28-29 and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 2003/0007954), in view of Atala et al. (US Patent 6,479,064), MacLaughlin et al. (US Patent 6,692,738), and further in view of Springer et al. (2000), Rinsch et al. (2001) and Penn et al. (US 2004/0161412 A1, 60/405,274 and 60/424,065). Applicants respectfully disagree.

Naughton et al., Atala et al., Springer et al., Rinsch et al. and Penn et al. are described above. MacLaughlin et al. describe implantable tissue matrices seeded with genetically engineered cells.

The Office Action asserts that Naughton et al. does not disclose the use of hydrogel or decellularized tissues as scaffold materials and further cites Maclaughlin et al., as well as Atala et al., Springer et al., Rinsch et al. and Penn et al. to remedy the deficiencies. However, combining Naughton et al. with the other references still does not reconstruct the claimed invention of the current application, that includes transiently transfecting a first population to express an angiogenesis modulating agent, culturing a *second population of cells* on a *matrix material* to produce an organ construct and *implanting the organ construct with the first population* of cells whereby *assimilation and differentiation of the second population* of cells occurs at the target site.

The Examiner states that "because Naughton et al., MacLaughlin et al. and Atala et al. all disclose scaffold materials which are appropriate for formation of engineered tissue constructs, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute any of the scaffold materials for another."

However, the Office Action fails to recognize that the references combined with Naughton still do not yield the invention of claim 23 or dependent claims therefrom. Moreover, the Office Action fails to provide a reason why one of ordinary skill in the art would combine the elements in the same way as the claimed new invention. As hindsight reconstruction is improper the Office Action has improperly rejected the Applicants' invention.

Furthermore, as noted above, Naughton actually *teaches away* from the use of a *separate population* of cells genetically engineered to *transiently express angiogenesis modulating agents*. The previously presented arguments are incorporated by reference in the interest of brevity.

Therefore, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection to claims 23-26, 28-29 and 33-37.

CONCLUSION

In view of the above remarks, Applicants' respectfully request reconsideration and allowance of the application. The Examiner is invited to call the undersigned at (617) 439-2948 if there are any questions.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 141449, under Order No. 105447-0002.

Respectfully submitted,

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